IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : William Alejandro THOMPSON

Group Art Unit : 1611

Appl. No. : 10/820,694

Examiner : Isis A.D. GHALI

Filed : April 9, 2004

Confirmation No. : 8732

For : TRANSDERMAL DELIVERY COMPOSITION

DECLARATION OF LAURA SPAULDING
PURSUANT TO 37 C.F.R. §1.132

I, Laura SPAULDING, declare that:

1. I am a co-sponsor of the above-identified U.S. Patent Application No. 10/820,694, filed April 9, 2004, entitled TRANSDERMAL DELIVERY COMPOSITION. I am currently a Senior Principal Scientist at a U.S-based company with supervisory authority over a laboratory staff involved in researching and developing innovative approaches to skin care, i.e., sunscreen, products. Previously I helped establish Coughlan Products Corporation as a competitive personal care contract manufacturer with custom formulation capability that specializes in technologies regarding direct compression tablets, effervescing & noneffervescing powders, salts, body scrubs, massage oils, and hot pours. I have over thirty years experience as a research and development scientist/manager in diversified areas of consumer products and pharmaceutics, including powder and tablet formulations and effervescent technology. I have a Bachelor of Science degree in Chemistry from Montclair State College. I obtained a Master of Science and Doctor of Philosophy degrees, both in Inorganic Chemistry, from Seton Hall University. Based on all of the above training and experience, I am a specialist in, among other things, the fields of inorganic chemistry, powder and tablet formulations, as well as effervescent technology.

2. I have reviewed the above-identified patent application as filed, as well as the claimed subject matter as set forth in the Amendment submitted March 15, 2010 in response to the Office Action mailed on September 15, 2009.

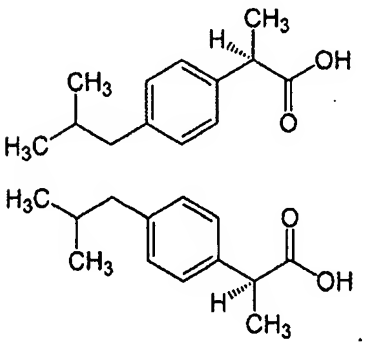
3. In 2004, during my employ at Coughlan Products, I formulated a direct compression, effervescent bath tablet composition that could be used on high speed rotary presses and single-punch presses using a novel premix supplied by NENE Labs. The materials in the premix included clarified sesame oil, isopropyl myristate, and ibuprofen.

4. Very surprisingly, the solubility of ibuprofen in vegetable and nut oils was observed to vary greatly. Solubility in clarified sesame oil was greatly preferred because at very low temperatures such as 40°C a clear, super-saturated system with ibuprofen could be made. In particular, when equal amounts of ibuprofen were added to mixtures of clarified sesame oil isopropyl myristate, almond oil and isopropyl myristate, or olive oil and isopropyl myristate, the ibuprofen was found to dissolve readily at 40°C in the clarified sesame oil mixture. Furthermore, the ibuprofen remained completely dissolved after cooling back to room temperature, and remained completely dissolved for 24 hours thereafter. Attachments A-E are color images evidencing the super-saturation of ibuprofen in clarified sesame oil as compared to almond oil and/or olive oil. In each image with three flasks, the clarified sesame oil mixture is on the left, the almond oil mixture is in the center, and the olive oil mixture is on the right. Notebook pages evidencing the amounts of ibuprofen, isopropyl myristate, and each type of oil used in each mixture, as well as the procedure for dissolving the ibuprofen in each mixture are also attached.

5. The following aspects are unique to the combination of clarified sesame oil and ibuprofen.

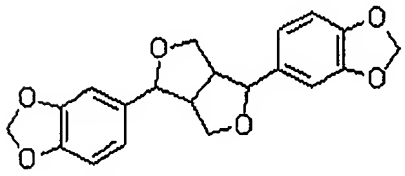
(a) First, ibuprofen is a non-steroidal anti-inflammatory drug also known as

iso-butyl-propanoic-phenolic. The chemical structures below show that ibuprofen exists as a mixture of R and S isomers. The combination of very slight water solubility and its inherent acid functional group make this particular compound an excellent candidate for effervescent tablets.

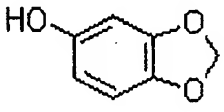


Ibuprofen in an effervescent tablet and as part of the effervescent mechanism helps to more uniformly disperse the ibuprofen throughout the bath water, and achieve overall body transdermal absorption.

(b) Second, monounsaturated and polyunsaturated fatty acids common to other vegetable and nut oils are present in sesame oil in different proportions. Second, unique to clarified sesame seed oil is the presence of unsaponifiables such as two natural antioxidants called sesamin and sesamol, shown below.



Sesamin



Sesamol

Not to be held to anyone theory, it appears the presence of sesamin and sesamol help dissolve ibuprofen into the sesame oil and allow the dissolution of ibruprofen in sesame oil to a super-

saturation point. In particular, sesamin and sesamol contain a high degree of polarity and conjugated double bonds similar to ibuprofen that would enable solubilization on the classic theory of "like dissolves like." A third unsaponifiable species, called sesamoline, may also assist in ibuprofen transdermal absorption though the skin.

6. In light of all the above, the combination of sesame oil and ibuprofen in the presently claimed formulation quite unexpectedly provides an oil phase containing super-saturated ibuprofen. Furthermore, the super-saturation provides unexpectedly enhanced transdermal delivery potential.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application and any patent issuing thereon.

Date: March 23, 2010

Laura SPAULDING, Ph.D.
7 Lockley Court
Wayne, NJ 07470

LAURA A. SPAULDING, Ph.D.

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Wayne, NJ 07470

Residence
973-790-5684

SUMMARY

Over thirty years experience as a research and development scientist/manager in diversified areas of consumer products and pharmaceutics. Also exhibits excellent formulation, supervisory, and communication skills with proven ability to interact effectively with all levels of management, staff, and clients. Key experience and skills in the following:

- AP/Deo Formulations
- Candle Formulations
- Fragrance Technology
- Insecticidal Formulations
- Hard Surface Cleaners
- Powder & Tablet Formulations
- Effervescent Technology
- Sunscreen Formulations
- Manufacturing Scale-Up
- GMP Stability Program
- GMP Dissolution Laboratory
- Sterile Process Validation
- Statistical Data Analyses
- FDA Pre-Approval Inspections
- US & Int'l Registration Support
- Patents
- Project Management
- Staff Supervision

PROFESSIONAL EXPERIENCE

ENERGIZER PERSONAL CARE, Allendale, NJ
Senior Principal Scientist – Sun Care R&D **6/2006 – Present**

- Member of Advanced Technology Group identifying, researching, and developing innovative approaches to global Sun Care consumer needs utilizing internal and external resources.
- Initiated several CDA and JDAs with domestic and international companies to expand opportunities of designing novel compounds pertaining to enhancing performance of sunscreen active materials.
- Actively supported both Hawaiian Tropic and Banana Boat marketed brands. Developed and launched SPF VWR 80 and 100 lotions, and in development is the SPF VWR 100 standard aerosol spray. Utilized Labsphere UV 2000S, Dual Con, Anton Par Physica 301 Rheometer.
- Supervise Lab Staff of 2 people.

COUGHLAN Products Corp., Wayne, NJ
Vice President – R&D, QC, Safety **1/1998 – 5/2006**

- Helped establish company as a competitive personal care contract manufacturer with custom formulation capability that specializes in technologies regarding direct compression tablets, effervescing & non-effervescing powders, salts, body scrubs, massage oils, and hot pours.
- Introduced the use of various grades of sugar crystals & beads, Epsom salts, sea salts, vitamins, minerals, extracts, botanicals, oatmeal, mustard, soy, additives to create milk baths water softeners, skin care emollients, etc. and proper dispersion of lake dyes.
- Developed, implemented & continually maintain formulation technology program, fragrance approval program, QC program, SOP program, Stability program, and Safety program
- Conduct on-site & off-site presentations/forums to current and prospective customers.
- Supervise Lab Staff of 4 people and QC Staff of 4 people.

NOVILLE, Inc., South Hackensack, NJ
Sr. Research Scientist - Creative Applications **7/1996 - 10/1998**

- Researched, identified & implemented new product formulation technologies and fragrance technologies to enhance finished product aesthetics and performance. Key product areas included antiperspirants, deodorants, candles, and room fresheners.
- Three patents issued which helped define Noville as a leader in clear candle technology, which ultimately lead to increased fragrance sales.
- Worked closely with perfumers, fragrance evaluators, and analytical personnel.
- Participated in on-site & off-site presentations/forums to current and prospective customers.

AMERICAN CYANAMID CO., Pearl River, NY
Principal Scientist - STORZ Ophthalmic Research **6/1993 - 5/1996**

- Researched, identified & implemented a GMP stability program designed for the STORZ Ophthalmic Research Division to meet current/proposed FDA and ICH Guidelines. Includes identification of stability information database, initial enhancements, PC network, environmental chambers, and related SOPs to support stability operations.
- Completed preparations for several Pre-Approval Inspections of current stability database and reports for Lederle Quality Audits & FDA Compliance Office. Interacted with various regulatory, analytical, and formulation departments to resolve issues.
- Prepared comprehensive stability reports with shelf-life recommendations to support IND & NDA filings, justification of specifications, set retest/expiry dating for clinical supplies.
- Participated in total validation of the Formulations Research Stability Information Management System (FRSIMS 3.1) made necessary by hardware and software upgrades.
- Monitored analytical workflow of on-going stability studies, prioritized workload, trouble-shooted stability/analytical situations.
- Completed formulation activities for two sterile ophthalmic solutions. Issued report detailing all pharmaceutic development activities and manufacturing process recommendations.
- Designed & conducted validation protocols for the manufacture of sterile ophthalmic solutions in compliance with GMPs. Issued approved validation reports detailing the SOI, SOPs, statistical treatment of in-process and analytical data, cleaning validation, and media fill studies.

Group Leader - Medical Research Division, Formulations Research **10/1990 - 5/1993**

- Managed and coordinated the development and operation of the GMP Stability Program, the Dissolution Development Laboratory, and activities of 12 professional & technical personnel.
- Initiated the use of statistical analyses of stability data to project expiration date; rationally determined and justified release and shelf-life specifications.

- Introduced and Chaired the Workflow Management Task Force; a forum for Stability Coordinators and Analytical Group Leaders to discuss, plan, make recommendations regarding test backlog situations, workload forecast, scheduling of new batches, clinical & special studies support, technology transfer of methods, protocol compliance and monograph issues.

- Interacted with other Sections & Divisions: Formulations Research, Regulatory, QC, Analytical Services, Manufacturing, Chemical Research, Toxicology, Clinical Research, Statistics, & Marketing. Instrumental in influencing and coordinating efforts to expedite product submissions.

- Interacted with FDA Compliance Inspectors during several Pre-Approval Inspections, presented to FDA (Oncology), responded to FDA and BOH queries and deficiencies, compiled comprehensive stability & specification reports to support domestic and international filings.

- Managed GMP dissolution and particulates testing to support stability, clinical leads, and Lederle line extension work. Included formulation screening, methods development and validation, support of stability protocols, clinical release testing, comparative agent testing, specification setting, and specialized analytical support for formulation development.

- Maintained electronic archiving of stability & dissolution reports, as well as chromatographic and particulates testing raw data via SIMS, LANtastic, PC network, and Macintosh.

- Managed an annual budget of $1.5 million in a cost effective and flexible manner to meet changing needs of the company and the BOH's worldwide.

AMERICAN CYANAMID CO., Clifton, NJ
Group Leader - Household Products **1/1990 - 9/1990**

- Developed two next generation PINE-SOL liquid cleaner emulsion formulas to meet use dilution disinfectancy and improved deodorization objectives. Provided documentation for EPA registration of both compositions. Discovered proprietary antimicrobial system.

- Responded quickly to issues concerning biodegradability of formulas; use of Bittrex; cost reduction measures for closure resins, colorants and liners; claims substantiation; competitive product assessments; new raw material approval and alternate sourcing.

- Performed appropriate duties as Study Director. Prepared and issued Study Protocols, Study Schedules, Final Reports, & SOPs in compliance with GLPs mandated by the EPA.

- Managed staff of 6, conducted performance appraisals and salary administration, worked closely with applied research service groups, conducted in-house consumer testing, and an R&D Screen. Resolved manufacturing issues, and participated in various marketing and market research activities.

Group Leader - Insecticides Research **1/1988 - 12/1989**

- Developed compatible line extension products. Provided support for national launch of COMBAT Room Fogger and COMBAT Ant & Roach Instant Killer aerosols, and MAXFORCE Pharaoh Ant Killer Bait for the consumer and PCO markets.

- Completed feasibility assessments of vendor formulations for selection of COMBAT Flea Fogger and Flea & Tick Pump Spray products. Conducted appropriate product development activities to support 1990 test market focusing on "Kit" approach to flea control.

- Managed all COMBAT and MAXFORCE brand maintenance activities. Included claims substantiation, competitive product testing in lab and field, alternate sourcing of raw materials for bait and tray, insectary maintenance, identification of new leads to enhance COMBAT efficacy performance, and responding to numerous regulatory, manufacturing and cost reduction issues.

- Managed staff of 6, conducted performance appraisals and salary administration, coordinated activities of outside cooperators and consultants, and fully utilized R&D support groups. Worked closely with the marketing and market research groups.

Project Leader/Senior Chemist - Household Products **2/1985 - 12/1987**

- Conducted various laboratory studies and completed appropriate documentation for the development, registration, and manufacture of Broad Spectrum PINE-SOL (emulsion).

- Coordinated activities and participated in the development of a non-pine, emulsified liquid cleaner, oven cleaner, and paint remover products.

- Supervised staff of 4 and interacted with various R&D support groups, marketing and market research personnel.

SETON HALL UNIVERSITY, South Orange, NJ
Teaching Assistant - Chemistry Department **1/1983 - 1/1985**

AMERICAN CYANAMID CO., Clifton, NJ
Chemist - Discovery Research **6/79 - 12/82**

- Formulated and developed new pesticide products including COMBAT/MAXFORCE Roach Control System and COMBAT Ant Control System.

- Provided support for pilot plant scale-up, R&D Screens, focus groups, field studies, EUP and EPA registrations, competitive product assessments and claims substantiation.

- Supervised 2 full-time and 2 part-time staff.

PATENTS

US Patent 4,845,103	COMBAT Roach Control System
US Patent 4,867,898	Broad Spectrum PINE-SOL
EP Patent 467,618	Broad Spectrum PINE-SOL II
US Patent 5,843,194	Clear Liquid & Semi-Solid Candles
US Patent 5,871,553	Clear Tart Candle
US Patent 5,882,363	Clear Pillar Candle
US Patent 6,054,517	Clear Pillar Candle II

PROFESSIONAL AFFILIATIONS

AWARDS/SPECIAL RECOGNITION

1994 Achievement Recognition for Validation and Product Launch of OCUCOAT Products
1993 Special Recognition for Contributions to FDA Approval of TAZOSYN Products
1993 Special Recognition for Contributions to FDA Approval of SUPRAX Plastic Bottle Conversion
1992 Special Recognition for Contributions to Photofrin European Submissions
1992 Special Recognition for Specification Work on l-Leucovorin Products
1987 Creativity Award for Broad Spectrum Antimicrobial System in Pine Oil Cleaners
1986 Creativity Award for Broad Spectrum Antimicrobial System in Hard Surface Cleaners
1982 Commendation for Development of COMBAT Products
1981 Commendation for Splash Pattern/Eye Irritancy for Alkaline Hard Surface Cleaners

SHORT COURSES

2009 Coaching for Excellence, Energizer Internal Course
2009 Targeted Selection Interviewing, Energizer Internal Course
2008 ACS Dispersions in Liquids: suspensions, Emulsions, and Foams
2008 Silicone Emulsifier Workshop, Tony O'Lenick, Siltech Industries
2006 SCC Practical Basics & Theory in Emulsion Technology
2006 Creative Problem Solving, Playtex Products Internal Course
2006 Polymers in Cosmetic Science, Webinar, University Southern Mississippi
1994 AAPS Workshop on Stability Guidelines for Testing Pharmaceutical Products: Issues and Alternatives II
1993 AAPS Workshop on Stability Guidelines for Testing Pharmaceutical Products: Issues and Alternatives I
1993 AAPS Optimizing the Commercialization Process for Biologically Derived Products
1993 Advances in Tablet Technology Workshop, Dr. A. Sakr, University of Cincinnati
1992 Validation by Design, Mr. Lynn D. Torbeck & Associates
1991 Drug Product Stability and Shelf Life, Dr. C. Rhodes, Continuing Education
1990 Management of Technical Projects, New York University
1989 Managing Laboratory Personnel, New York University

EDUCATION

Doctor of Philosophy	Seton Hall University	May 1985	Inorganic Chemistry
Master of Science	Seton Hall University	May 1983	Inorganic Chemistry
Bachelor of Science	Montclair State College	May 1979	Chemistry

PUBLICATIONS

L. Spaulding and H.G. Brittain, "Intermolecular Energy Transfer Between Lanthanide Complexes. 8. Tb(III) Done and Eu (III) Acceptor Complexes of Citric Acid", Journal of Luminescence, 28, 285 (1983).

H.G. Brittain, R. A. Copeland, M. Ransom, and L. Spaulding, "Terbium (III) Complexes of (-)-Quinic

Acid", Journal of Less Common Metals, 94, 393 (1983).

L. Spaulding and H.G. Brittain, "Intermolecular Energy Transfer Between Lanthanide Complexes. 9. Terbium (III) Donor and Europium (III) Acceptor Complexes of Amino Polycarboxylic Acids", Inorganic Chemistry, 22, 3486 (1983).

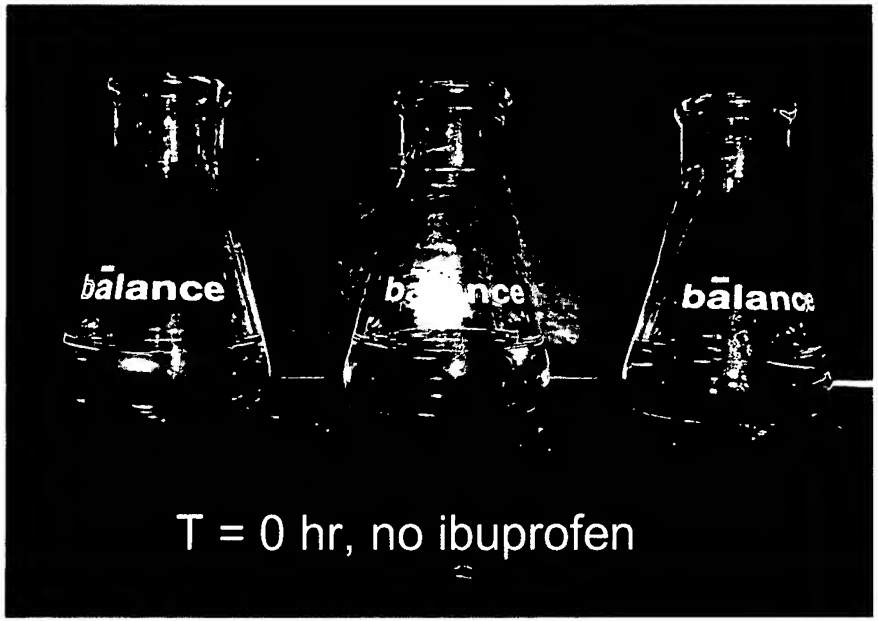
L. Spaulding and H.G. Brittain, "Solution Chemistry of Lanthanide Complexes. 7. Tb(III) and Eu (III) complexes of (S,S)-Ethylenediamine-N,N'-disuccinic Acid", Inorganic Chemistry, 23, 2165 (1984).

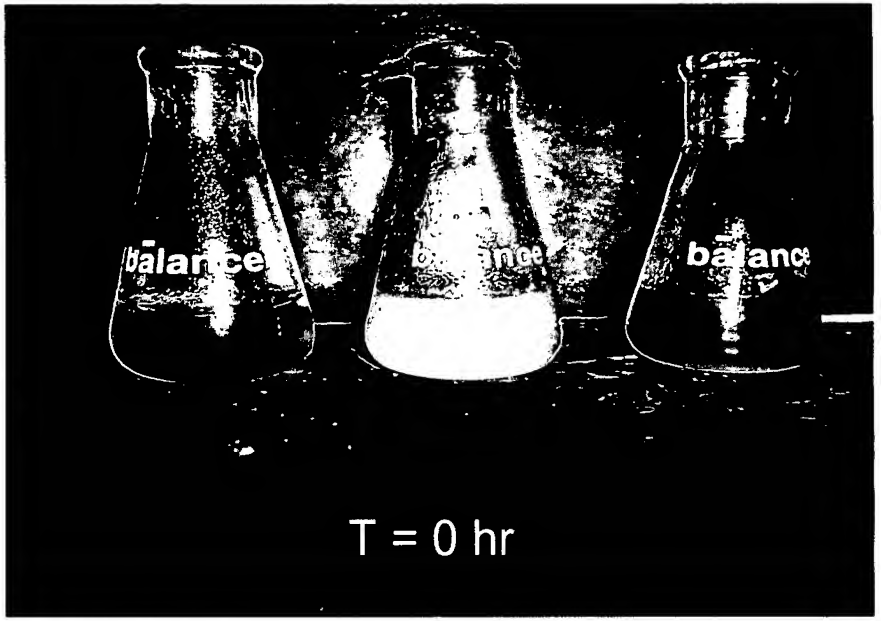
L. Spaulding and H.G. Brittain, "Complexation of Amino Acids by Terbium (III) Ethylenediamine-tetraacetate", Inorganic Chemistry, 24, 3693 (1985).

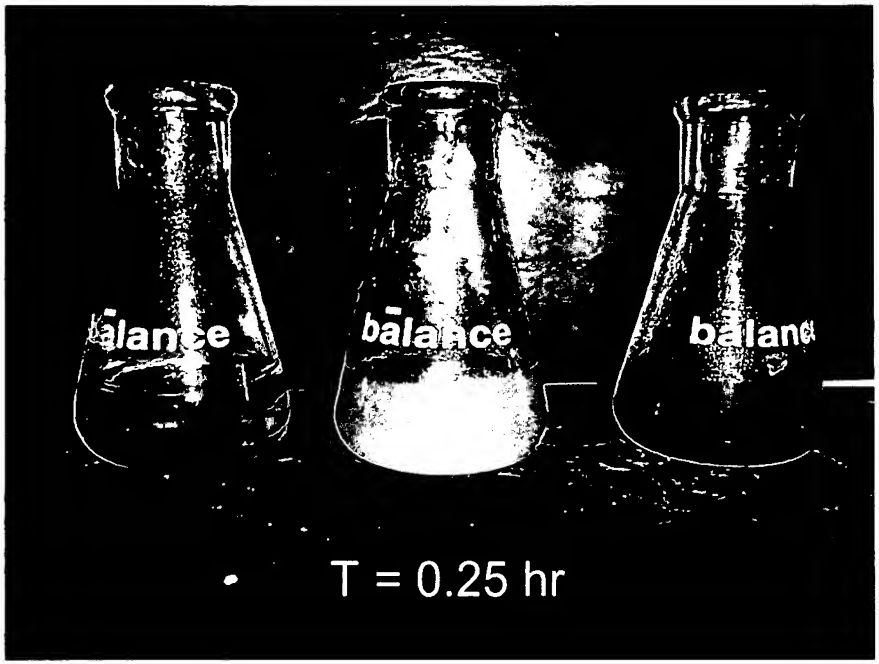
L. Spaulding and H.G. Brittain, "Circularly Polarized Luminescence Studies of the Ternary Complexes Formed by Terbium (III) with (S,S)-Ethylenediamine-N,N'-disuccinic Acid and Achiral Substrate Ligands", Inorganic Chimica Acta, 110, 197 (1985).

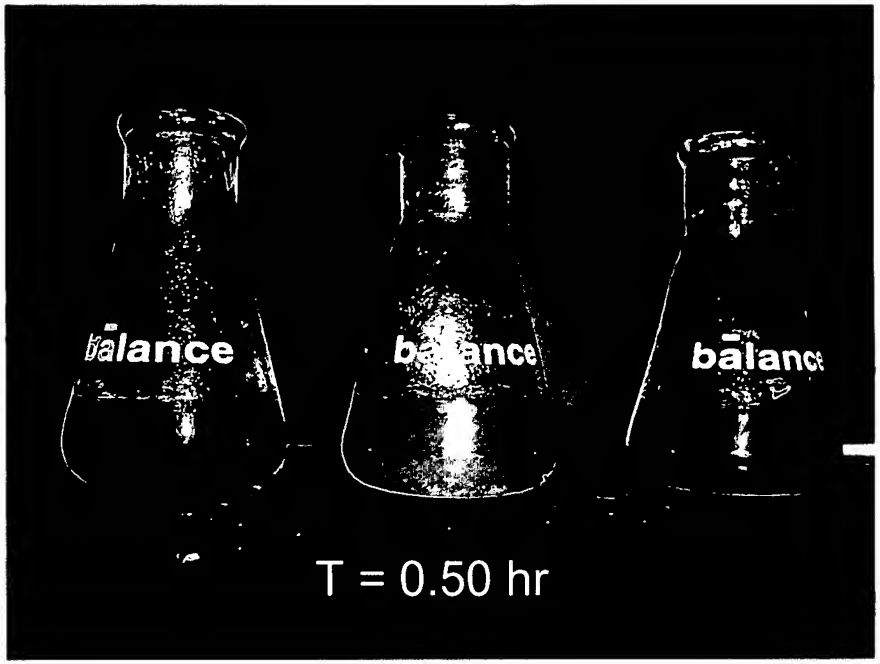
L. Spaulding and H.G. Brittain, "Circularly Polarized Luminescence Studies of the Ternary Complexes Formed by Terbium (III) with Chiral Amino Polycarboxylates and Achiral Substrate Ligands", Inorganic Chemistry, 25, 188 (1986).

L. A. La Marca Spaulding, "Circularly Polarized Luminescence Studies of Lanthanide Aminopolycarboxylate Complexes", Dissertation Abstracts International, 46, 3841 (1986).









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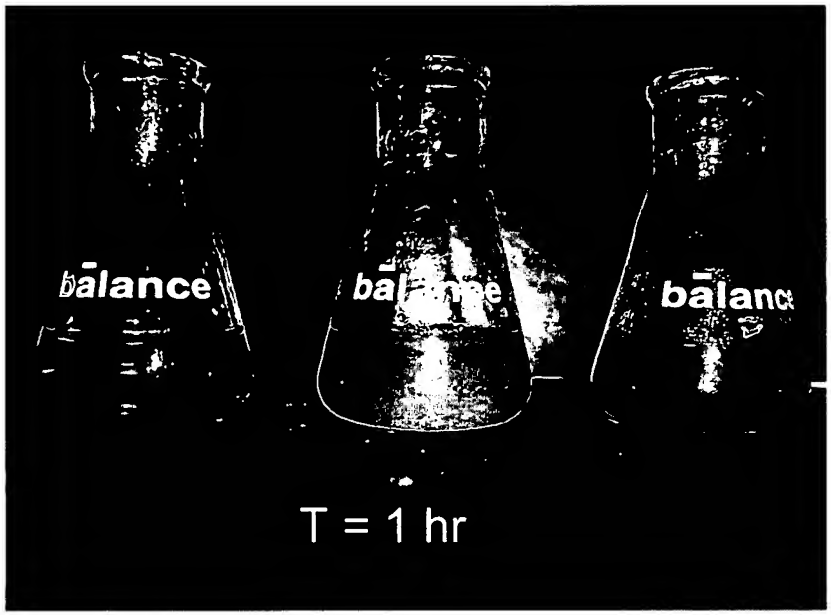
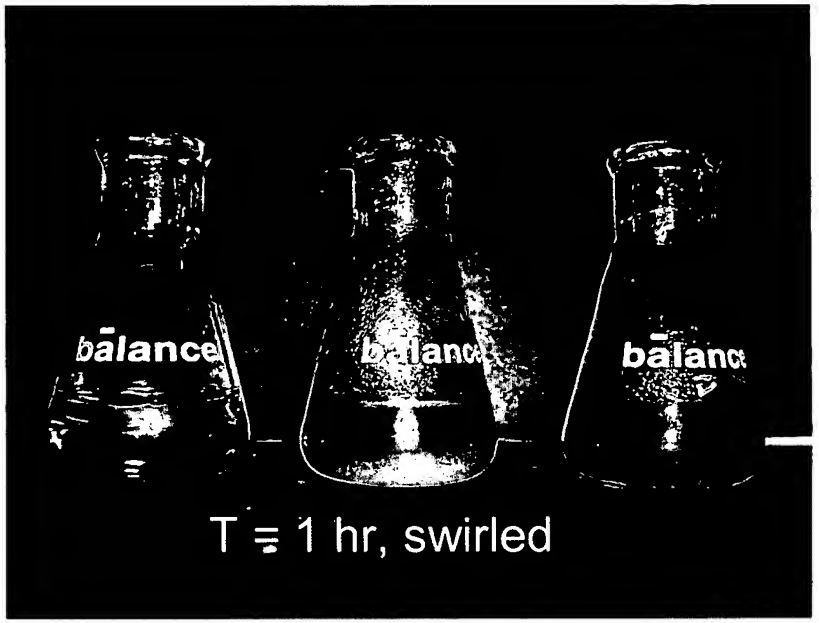

bālance
bālance
bālance
T = 1 hr


bālance
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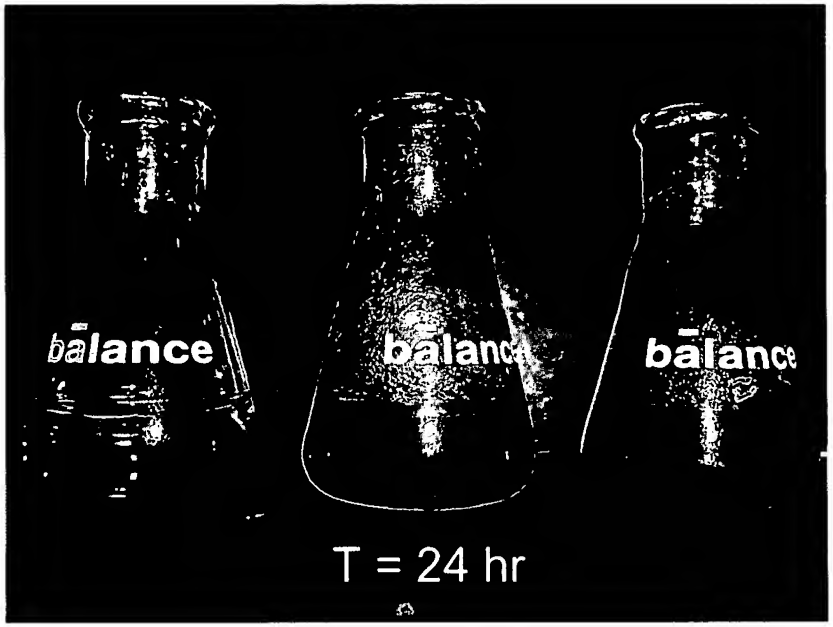
T = 1 hr, swirled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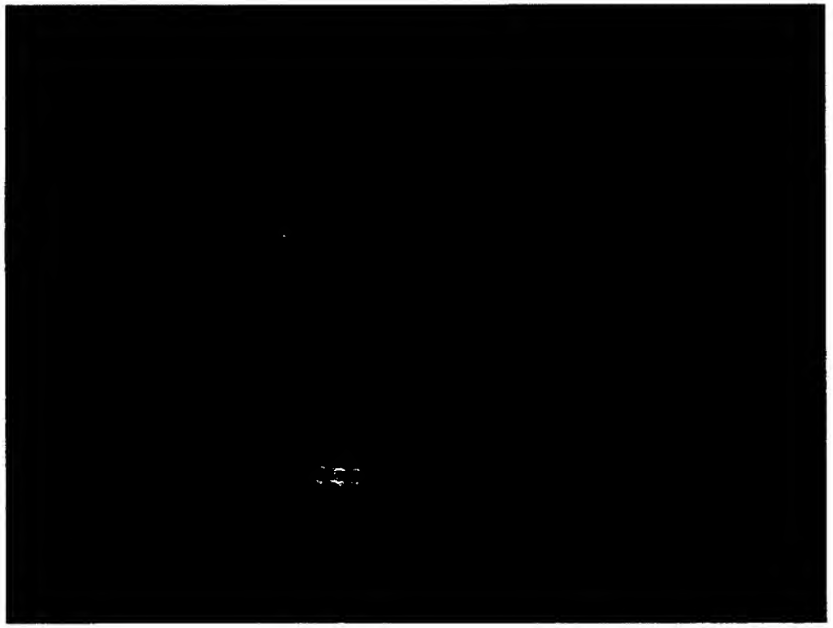
T = 24 hr

B

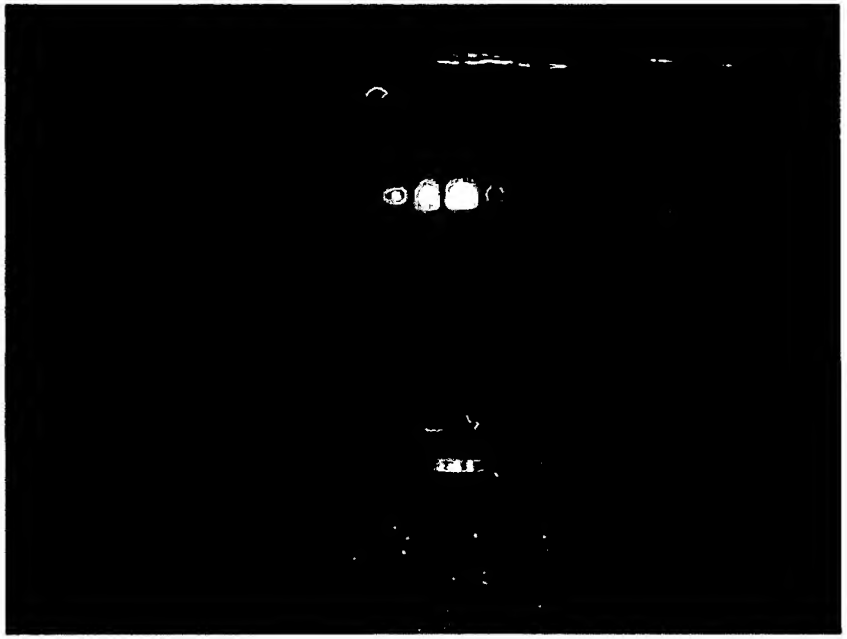
Almond oil, isopropyl myristate,
and ibuprofen at 1 hr.

C



Olive oil, isopropyl myristate, and ibuprofen at 1 hr.

D



Sesame oil, isopropyl myristate,
and ibuprofen at 1 hr.

E

14 Sept 2009

Solubility of Ibuprofen in oil mixture with ISP.

Procedure:

Clarified sesame oil (clarified)	10.8g w/w
Isopropyl Myristate (ISP)	7.6g w/w
Ibuprofen USP	9.8g

1. Mix clarified sesame oil in small flask with ISP.
2. Heat oil mixture to 40°C and add ibuprofen and stir until mixture is clear.
3. Allow to cool back to room temperature
4. Watch/Observe solution at T = Ø, T = 15 min, T = 30 min, T = 1 hour

Observations:

Ibuprofen dissolves readily at 40°C. This temperature is used so as to not produce esters of ibuprofen.

At T = Ø = clear solution
T = 15 min = "
T = 30 min = "
T = 1 hr "

14 Sept 2009

Part II Almond oil mixture

Procedure:

Sweet Almond Oil USP	10.8g w/w
Isopropyl myristate	9.6g w/w
Ibuprofen USP	9.8g

1. Mix sweet almond oil with isopropyl myristate until mixture is homogeneous in small flask
2. Heat mixture to 40°C and add ibuprofen and stir until solution is clear.
3. Allow solution to cool to room temperature and
4. Observe at T=Ø, T=15min, T=30 min, T= 1 hour

Observations:

The ibuprofen goes into solution after a few minutes.
Some residual is noticed on flask bottom.

T= Ø clear solution with residual on bottom.
T= 15 min clear solution with residual on bottom.
T= 30 min clear solution but with significant crystal formation (precipitate)
T= 1 hour clear to cloudy solution with crystal formation

19 Sept 2009

Part III Olive oil mixture

Procedure:

Olive oil N.F.	10.8 g	w/w
Isopropyl myristate	9.6 g	w/w
Ibuprofen USP	9.8 g	

1. Mix Olive oil N.F. with isopropyl myristate in small flask until mixture is homogeneous.
2. Heat mixture to 40°C and add ibuprofen and stir until solution is clear
3. Allow solution to cool to room temperature and
4. Observe at T= Ø, T= 15 min, T= 30 min, T= 1 hour.

Observations:

The ibuprofen dissolves readily with stirring, although there is a filmy residual on flask bottom.

T= Ø	Clear solution with light film on flask bottom
T= 15	Solution appears cloudy. Film on flask bottom unchanged
T= 30	More cloudiness in solution. Thicker film on flask bottom.
T= 1 hour	Cloudy, thick film. Crystal formation evident.